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Practice Variation in Triple Therapy for Patients With Both Atrial Fibrillation and Coronary Artery Disease

Insights From the ACC's National Cardiovascular Data Registry

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ABSTRACT

OBJECTIVES The aim of this study was to test the hypothesis that in the United States substantial practice variation exists in triple therapy prescribing practices, unrelated to measured patient factors.

BACKGROUND Recent data have shown that the risk of bleeding on dual antiplatelet therapy and oral anticoagulation ("triple therapy") is high, although the optimal strategy for patients with atrial fibrillation and coronary artery disease remains unclear.

METHODS Using the PINNACLE (National Practice Innovation and Clinical Excellence) registry, we identified 79,875 unique patients with both atrial fibrillation/atrial flutter and myocardial infarction and/or coronary stenting within 12 months. Using triple therapy as a binary outcome variable, we created a mixed-effects logistic regression model with patient factors as fixed effects and practice site as a random effect. Patient factors included age, sex, diabetes, congestive heart failure, hypertension, peripheral arterial disease, prior stroke or transient ischemic attack, history of systemic embolization, and dyslipidemia. The model was assessed with a median odds ratio to assess practice variation after adjustment for patient factors.

RESULTS After adjustment for patient factors, significant practice variation was suggested by a median odds ratio of 2.78 (95% confidence interval: 2.33 to 3.23). In particular, this suggests that 2 randomly selected practices would differ in their likelihood of prescribing triple therapy for an identical patient by a factor of nearly 3.

CONCLUSIONS In the United States, there is substantial practice variation in prescribing triple therapy to eligible patients even after adjustment for patient clinical characteristics. These results suggest that opportunities exist to improve the quality of care of this sizable population. (J Am Coll Cardiol EP 2016;2:36–43)

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The management of patients with indications for both antiplatelet and anticoagulant therapy has generated controversy. For patients with a history of myocardial infarction (MI) within 1 year or percutaneous coronary intervention (PCI) within 1 month for bare metal stents and within 1 year for drug-eluting stents, dual antiplatelet therapy (DAPT) is indicated to reduce the risk of adverse thrombotic events, including MI and stent thrombosis (1). Many patients with MI and/or PCI also have atrial fibrillation (AF). Of populations referred for elective PCI, 5% to 10% are taking oral anticoagulation before PCI (2), generally because of AF.

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Current guidelines for these patients list triple oral antithrombotic therapy with aspirin, clopidogrel, and warfarin as a class IIb recommendation ("may be considered") (3), reflecting a lack of clinical consensus. Before the creation and widespread dissemination of risk scores, variance in prescription rates for oral anticoagulation in patients with AF correlated with physician specialty, with different specialties developing different risk estimates for cardioembolic stroke (4,5). Even after the publication of the CHADS (congestive heart failure, hypertension, age 75 years, diabetes mellitus, stroke) score (6), variation among different regions in the United States over and above patient characteristics has persisted (7). Trials evaluating triple therapy have either been underpowered for stent thrombosis (8) or suggested that 6 weeks and 6 months of triple therapy were equivalent (9). As such, the optimal strategy remains unclear. In these circumstances, providers may rely on anecdotes and local peer-practice patterns. Assessing relative contributions of provider versus patient characteristics in determining treatment decisions has the potential to provide insight into the potential of higher quality evidence, stronger guidelines, and/or the systematic incorporation of personalized risk calculators into clinical practice.

Given the mixed evidence for treatment of patients with MI or PCI who require anticoagulation for AF, we sought to assess current practice in the United States for these patients. In particular, we assessed risk-adjusted variation in patterns of care in data from the American College of Cardiology National Cardiovascular Data Registry's PINNACLE (National Practice Innovation and Clinical Excellence) program, a prospective registry of outpatient cardiac care (10).

METHODS

STUDY POPULATION. We examined patient encounters in outpatient cardiology practices in the United States from the American College of Cardiology's PINNACLE registry. PINNACLE is the first national, prospective, office-based quality improvement registry in the United States (10). This voluntary registry incorporates a variety of clinical data from outpatient visits, including symptoms, vital signs, comorbidities, medications, and recent hospitalizations.

We identified 9,538,255 patient encounters in data from the PINNACLE registry from 2008 to 2013. We included the most recent patient encounter and identified patients with both MI within 12 months and/or coronary stenting within 12 months and with AF/atrial flutter. With those criteria, 79,875 unique patients were identified for inclusion. A flow diagram, showing exclusions, appears in **Figure 1**.

OUTCOMES AND COVARIATES. For each patient, we recorded all antiplatelet (aspirin, clopidogrel, prasugrel, ticlopidine) and anticoagulant (warfarin, dabigatran, rivaroxaban, apixaban) medications taken by the patient at the time of the visit. We then created a binary outcome variable representing triple therapy. We defined triple therapy as aspirin, at least 1 $P2Y_{12}$ receptor inhibitor, and at least 1 oral anticoagulant.

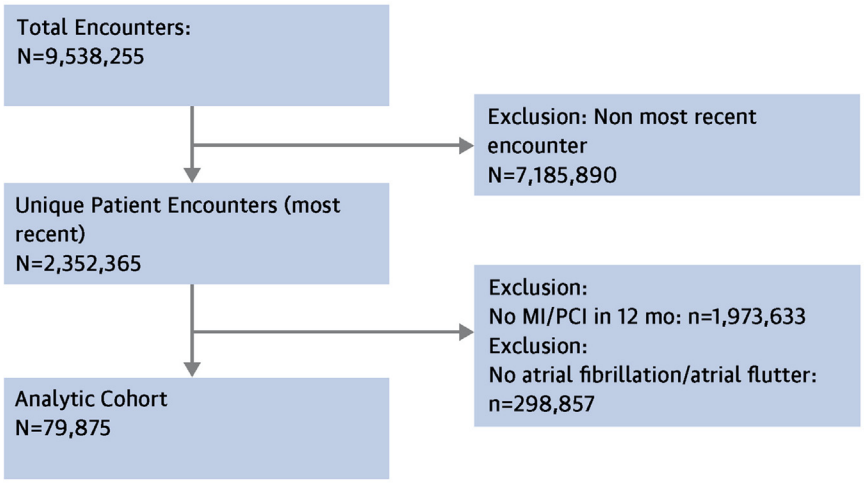
For each patient encounter, we extracted data on patient characteristics, including age, sex, race (white, black, native Hawaiian, American Indian, Asian), ethnicity (Hispanic, not Hispanic), insurance status (private, Medicare fee-for-service, Medicare health maintenance organization, Medicaid, military, state, Indian Health Service, non-US, none), comorbidities (hypertension, systemic embolization, heart failure, prior heart failure encounter within 12 months, stable angina, dyslipidemia, peripheral arterial disease, diabetes, prior stroke or transient ischemic attack [TIA]), and provider designation (MD, NP, other).

STATISTICAL ANALYSIS. Using the binary outcome variable of triple therapy versus no triple therapy, we proceeded with logistic regression with 2 mixed-effects models. The first model, the empty model, contained only practice site as a random effect and no fixed effects. The second model, the adjusted model, treated patient variables as fixed effects and individual practice as a random effect. In choosing the fixed effects, we identified variables associated

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation
DAPT = dual antiplatelet therapy
EHR = electronic health record
MI = myocardial infarction
MOR = median odds ratio
PCI = percutaneous coronary intervention
TIA = transient ischemic attack

FIGURE 1 Flow Diagram of Included and Excluded Patients



MI = myocardial infarction; PCI = percutaneous coronary intervention.

with the risk of stroke in AF, including age, sex, hypertension, diabetes, congestive heart failure, peripheral arterial disease, prior stroke or TIA, and history of systemic embolization (11). For both models, we assessed variation in rates of triple therapy with a median odds ratio (MOR) with cluster variance in which the cluster unit was the physician practice. The MOR provides a measure of cluster-level variance when a multilevel regression analysis is performed and is appropriate for assessing variation in a mixed-effects model (12). By convention, an MOR >1.2 suggests clinically significant variation in the outcome among the cluster unit even after adjustment for fixed effects (12). In this particular case, an MOR >1.2 suggests clinically significant variation in rates of triple therapy among different physician practices, even after adjustment for patient characteristics.

SENSITIVITY ANALYSIS. Because aspirin can be inconsistently captured from registry data derived from electronic health records (EHRs) (13), we conducted an identical analysis with the triple therapy outcome defined differently—as either documented triple therapy or patients on an antiplatelet and anticoagulant without explicit mention of aspirin in the EHR. Because the primary analysis defined triple therapy as: 1) aspirin; 2) another antiplatelet other than aspirin; and 3) an anticoagulant, the sensitivity analysis explored any potential effects of incomplete aspirin documentation on our findings.

This study was approved by the PINNACLE Research and Publications Committee of the National Cardiovascular Data Registry.

RESULTS

From our inclusion criteria, 79,875 eligible patients were identified. Of these patients, 40,165 had PCI (50.3%) and 39,710 had MI without PCI (49.7%). Of the 40,165 patients with PCI, 28,899 (72.0%) did not have MI in the past 12 months, consistent with elective PCI. Of the full included cohort, 3,568 patients (4.5%) were on triple therapy. Of the 76,307 (95.5%) not on triple therapy, 41,316 (54.1%) were not on anticoagulation and 65,937 (86.4%) were not on DAPT. Clinical characteristics of the patients, divided by triple therapy versus no triple therapy, are shown in **Table 1**. In univariate analyses, male sex ($p < 0.001$), native American ($p < 0.001$) or Asian race ($p = 0.03$), and hypertension, history of systemic embolization, heart failure, stable angina, dyslipidemia, peripheral arterial disease, diabetes, and prior stroke or TIA ($p < 0.001$ for all) were all associated with triple therapy in univariate analyses. Native Hawaiian race was associated with less triple therapy ($p = 0.018$).

INDEPENDENT PREDICTORS OF TRIPLE THERAPY AND PRACTICE VARIATION. After multivariable adjustment in the adjusted model, dyslipidemia, history of systemic embolization, prior stroke or TIA, peripheral arterial disease, male sex, diabetes, and

TABLE 1 Clinical and Demographic Characteristics of Included Patients

	Total (N = 79,875)	Triple Therapy (Yes/No)		p Value
		Triple Therapy (n = 3,568)	No Triple Therapy (n = 76,307)	
Demographics				
Age, yrs	72.9 ± 12.3	72.8 ± 10.4	72.9 ± 12.4	0.391
Male	47,593 (59.6)	2,460 (68.9)	45,133 (59.1)	<0.001
Race				
White	45,419 (92.7)	2,100 (92.7)	43,319 (92.7)	0.955
Black	2,455 (5.0)	129 (5.7)	2,326 (5.0)	0.127
Native Hawaiian	257 (0.5)	4 (0.2)	253 (0.5)	0.018
Native American	1,203 (2.5)	94 (4.2)	1,109 (2.4)	<0.001
Asian	585 (1.2)	38 (1.7)	547 (1.2)	0.030
Missing	30,903	1303	29,600	
Insurance				
Private	43,347 (59.3)	2,016 (60.7)	41,331 (59.3)	0.093
Medicare FFS	40,414 (55.3)	2,073 (62.5)	38,341 (55.0)	<0.001
Medicare managed care	8,042 (11.0)	355 (10.7)	7,687 (11.0)	0.554
Medicaid	4,232 (5.8)	235 (7.1)	3,997 (5.7)	0.001
Military	1,443 (2.0)	119 (3.6)	1,324 (1.9)	<0.001
State	538 (0.7)	45 (1.4)	493 (0.7)	<0.001
Indian Health Service	22 (0.0)	0 (0.0)	22 (0.0)	0.623
Non-U.S.	8 (0.0)	1 (0.0)	7 (0.0)	0.310
None	8,521 (11.7)	376 (11.3)	8,145 (11.7)	0.536
Missing	6,831	249	6,582	
Clinical characteristics				
Hypertension	72,903 (91.3)	3,329 (93.3)	69,574 (91.2)	<0.001
Systemic embolization	1,866 (2.3)	160 (4.5)	1,706 (2.2)	<0.001
Heart failure	36,336 (45.5)	1,970 (55.2)	34,366 (45.0)	<0.001
Heart failure encounter within 12 months	27,243 (34.1)	1,509 (42.3)	25,734 (33.7)	<0.001
Stable angina	12,074 (15.1)	907 (25.4)	11,167 (14.6)	<0.001
Dyslipidemia	58,127 (72.8)	3,055 (85.6)	55,072 (72.2)	<0.001
Peripheral arterial disease	17,351 (21.7)	1,207 (33.8)	16,144 (21.2)	<0.001
Diabetes	24,677 (30.9)	1,614 (45.2)	23,063 (30.2)	<0.001
Prior stroke or TIA	21,621 (27.1)	1,219 (34.2)	20,402 (26.7)	<0.001
Cardiac events				
History of MI	56,630 (70.9)	2,483 (69.6)	54,147 (71.0)	0.078
History of MI within 12 months	50,976 (63.8)	1,901 (53.3)	49,075 (64.3)	<0.001
History of CABG within 12 months	16,605 (20.8)	932 (26.1)	15,673 (20.5)	<0.001
History of valvular surgery within 12 months	3,765 (4.7)	157 (4.4)	3,608 (4.7)	0.366
History of heart transplant within 12 months	50 (0.1)	6 (0.2)	44 (0.1)	0.023
History of PCI with bare-metal stents within 12 months	12,451 (15.6)	778 (21.8)	11,673 (15.3)	0.001
History of PCI with drug-eluting stents within 12 months	27,408 (34.3)	1,913 (53.6)	25,495 (33.4)	<0.001

Values are mean ± SD or n (%).

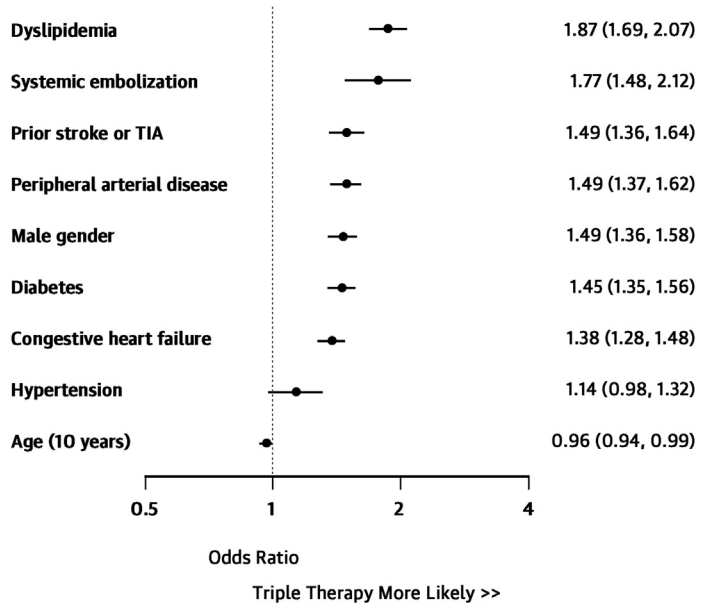
CABG = coronary artery bypass graft; FFS = fee-for-service; MI = myocardial infarction; PCI = percutaneous coronary intervention; TIA = transient ischemic attack.

heart failure were all independent predictors of triple therapy. Greater age was associated with reduced triple therapy. ORs of variables included in the model are shown in Figure 2.

VARIATION ANALYSIS. Unadjusted variation by practice is shown in Figure 3. In addition to patient-level variables treated as fixed effects in the adjusted model, we included practice site as a random effect and analyzed the mixed-effects model with an MOR. After adjustment for patient factors, significant practice variation was suggested by an MOR of 2.78 (95% confidence interval [CI]: 2.33 to 3.23). In the empty model, without adjustment for fixed effects (patient factors), the MOR was 2.84 (95% CI: 2.38 to 3.30).

SENSITIVITY ANALYSIS. In the sensitivity analysis, results were similar to those of the primary analysis, except age was not statistically significant. The MOR of the adjusted model was 2.49 (95% CI: 2.13 to 2.84) for the sensitivity analysis. The MOR for the empty model was 2.50 (95% CI: 2.14 to 2.85) for the

FIGURE 2 Predictors of Triple Therapy (Primary Analysis)



TIA = transient ischemic attack.

sensitivity analysis. ORs for the adjusted model in the sensitivity analysis are shown in Figure 4.

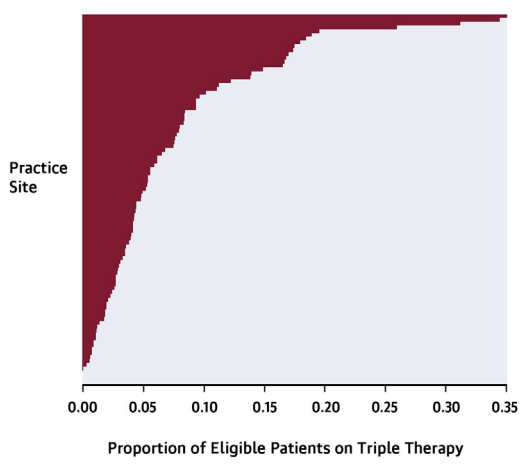
DISCUSSION

In a national registry of outpatients with cardiovascular disease, we demonstrated that after adjustment for patient characteristics, there was clinically significant variation at the practice level with respect to the treatment decision to prescribe triple therapy for patients who have indications for both DAPT and oral anticoagulation. The variation among practices remains similar even after adjustment for clinical variables. These results suggest that in these circumstances, physician practice style substantially influences clinical decision-making.

One institutional estimate suggested that 5% to 10% of patients undergoing elective PCI already take oral anticoagulation at the time of elective PCI (2). Our data suggest that in a national sample including a broad range of patients and clinical presentations, including acutely ill patients, even more patients with MI or PCI actually face this clinical dilemma after the MI or PCI. In particular, 21.1% of patients who had MI or PCI in the past 12 months also had AF or atrial flutter in the outpatient setting after the acute event or procedure. The higher proportion of patients with AF or atrial flutter may reflect a sicker, more acute population, with nearly two-thirds of patients with MI within the past year.

The optimal strategy in this clinical situation is uncertain and may vary for individual patients. In the WOEST (What is the Optimal Antiplatelet and Anticoagulant Therapy in Patients With Oral Anticoagulation and Coronary Stenting) trial, data were available for 279 patients assigned clopidogrel and warfarin and 284 patients assigned triple therapy (in this case, aspirin, clopidogrel, and warfarin). Over 1 year, the triple therapy group had more bleeding (44.4% vs. 19.4%; $p < 0.0001$). Strikingly, the group without aspirin had a trend toward lower rates of MI (3.2% vs. 4.6%; $p = 0.382$) and stent thrombosis (1.4% vs. 3.2%; $p = 0.165$) but the trial was not adequately powered for either endpoint. More recently, ISAR-TRIPLE (Triple Therapy in Patients on Oral Anticoagulation After Drug-Eluting Stent Implantation) trial compared 6 weeks of clopidogrel versus 6 months of clopidogrel in patients on aspirin and warfarin. The cumulative incidence of TIMI (Thrombolysis In Myocardial Infarction) major bleeding (5.3% vs. 4.0%; $p = 0.44$) or cardiac death, MI, stent thrombosis, or ischemic stroke (4.3% vs. 4.0%; $p = 0.87$) was similar for patients receiving 6 weeks or 6 months of clopidogrel (9). Despite these new trials, the optimal strategy for patients with indications for DAPT and oral anticoagulation continues to generate debate (14,15). Previous studies have shown that patient characteristics, including hypertension (16), lower age, and CHADS2-VASC risk score (17), correlate with the treatment decision for triple oral antithrombotic therapy in real-world

FIGURE 3 Unadjusted Proportion of Included Patients Prescribed Triple Therapy, By Practice Site



N = 93, excluding sites with fewer than 30 included patients.

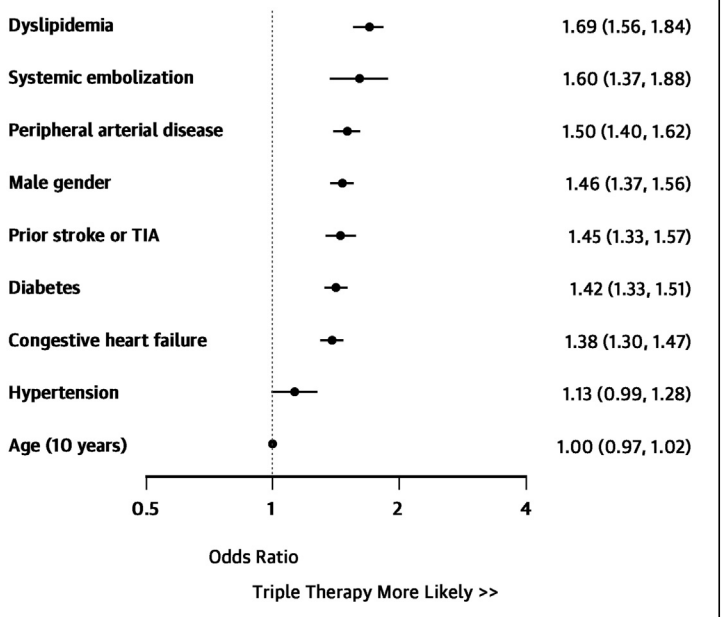
clinical practice. Our results confirm those results and extend them to establishing practice site as a major risk factor for the treatment decision.

Generally, our results show that variables that predict risk for stroke in AF and are included in the CHADS2-VASC score are correlated with triple therapy. Previous work had demonstrated an inverse relationship between stroke and continuation of warfarin for patients with non-ST-segment elevation MI, although that study was not restricted to patients with AF (18). More intense therapy is probably appropriate for higher-risk patients as a whole, given that thrombotic outcomes after PCI are worse for patients with higher CHADS2-VASC scores (19). Nevertheless, male sex was associated with higher propensity for triple therapy, although female sex has been associated with higher risk of stroke (20). This discrepancy may be related to female patients' higher risk of bleeding after PCI (21) or may be related to an undesirable risk-treatment paradox (male patients receiving more therapy despite their lower risk). Heart failure and diabetes are also risk factors for stent thrombosis (22) and were similarly associated with more triple therapy in our real-world analysis. We also demonstrated that dyslipidemia was associated with more triple therapy. Although dyslipidemia is not included in the CHADS2-VASC score, the overall higher risk for thrombotic events may have influenced this practice pattern.

Although this registry does not contain detailed information about patient risk for bleeding, some risk factors for bleeding were included in the analysis. The HAS BLED risk score for bleeding contains variables included in this registry (age, hypertension, and history of stroke) and variables not included in this registry (abnormal renal or hepatic function; bleeding tendency; labile international normalized ratio values; medications, including nonsteroidal anti-inflammatory medications; and alcohol abuse) (23). All 3 risk factors for bleeding captured in this analysis are also risk factors for thrombosis. Although the data available precludes a comprehensive assessment of patient bleeding risk, among these 3 risk factors for both thrombosis and bleeding, age was associated with less triple therapy and history of stroke was associated with more triple therapy. After multivariable adjustment, hypertension was not associated with triple therapy.

Even after adjustment for all of these patient-level factors, practice variation remained unchanged. In particular, with practice as a random effect, the MOR of 2.78 (95% CI: 2.33 to 3.23) suggests that 2 randomly selected practices would differ in likelihood of prescribing 1 unit more intensive therapy by a factor of nearly 3. Because residual variation among practices was unchanged after adjustment, we believe that these results demonstrate that in this scenario, provider effects determined treatment decisions more than patient factors. These findings of broad practice variation are consistent with surveys showing variation in interventional cardiologist approaches to patients with indications for anticoagulation receiving PCI (24).

FIGURE 4 Predictors of Triple Therapy (Sensitivity Analysis)



TIA = transient ischemic attack.

This substantial variation nationally by practice site is unlikely to represent optimal treatment for the large population of patients with coronary disease and AF. The publication of the DAPT trial may encourage longer courses of DAPT after PCI, which will heighten the relevance of this clinical situation (25). Nevertheless, clinicians have interpreted the results of the DAPT trial and other trials differently, with some advocating for at least 12 months of DAPT after PCI (26), and others suggesting that DAPT can sometimes be stopped before 12 months (27). This type of debate may lead to even more variation by practice site. Better clinical evidence and stronger guidelines for patients with both coronary disease and indications for oral anticoagulation may help. Even before higher-quality evidence is available, tools, including standardized clinical assessment and management plans, can standardize care norms based on evolving clinical

consensus (28). Secondly, establishing risk thresholds for bleeding and ischemic events might identify patients at risk for both and better inform the triple therapy therapeutic decision. Thirdly, this practice variation suggests that wider use of automated, standardized risk calculators could harmonize treatment decisions with patient risk profiles for both thrombosis and bleeding. Finally, identifying practices with either very high or very low risk-adjusted rates of triple therapy may be excellent targets to study the clinical outcomes of those treatment decisions. Because we have demonstrated that more than one-fifth of patients with PCI or MI also have AF, these types of efforts have the potential to substantially improve quality of care and patient safety nationally.

STUDY LIMITATIONS. Because aspirin is sometimes not captured within the EHRs, we may have underestimated the proportion of patients with triple therapy. Nevertheless, we are reassured by the result of our sensitivity analysis, which did not substantially change our results. Because PINNACLE is a voluntary registry, our results only reflect participating practices, making our results subject to bias. Nevertheless, there is no particular reason to suspect that voluntary participation in a quality registry would substantially correlate with propensity to prescribe triple therapy or propensity not to prescribe triple therapy. Because PINNACLE captures outpatient visits, we cannot reliably link these data to procedural data (such as angiographic characteristics associated with risk for stent thrombosis) or clinical outcomes such as major adverse cardiovascular events and bleeding. Because the clinical variables in PINNACLE were collected at the most recent office visit rather than at hospital discharge, AF could have developed after discharge. Nevertheless, the clinician could still change the treatment decision and opt for triple therapy at that time. We did not examine different strategies for warfarin management, including potentially lower international normalized ratio goals, which was out of scope for this analysis. We do not have information in PINNACLE about anticoagulants in investigational clinical trials, such as edoxaban, during this time period. Because these drugs were not widely available during this time, we are reassured that the number of patients in PINNACLE taking them was likely very small. Because the race variable was missing for nearly one-half of the patients in PINNACLE, we could not draw reliable conclusions about any influence of race on treatment decisions or access to care. Finally, although we adjusted for several patient factors, we cannot detect all clinical factors that could influence treatment decisions. In particular, we did not have access to patient bleeding history or some clinical risk factors for bleeding. Therefore, part of the practice site variance that we demonstrated may be related to unmeasured patient factors that are unevenly distributed among practices.

CONCLUSIONS

We have demonstrated that substantial practice variation exists in the triple therapy treatment decision for patients with recent MI or PCI and AF. These results suggest that focusing on this large population holds substantial promise for quality improvement nationally.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Substantial variation exists among practices nationally in the treatment decision for triple therapy in patients with indications for DAPT and oral anticoagulation, even after adjustment for patient characteristics.

TRANSLATIONAL OUTLOOK: Efforts should be directed to improve care nationally by developing a better understanding of the risks and benefits of triple therapy, establishing stronger clinical consensus about treatment decisions, and customizing treatment decisions to patients' individual risk profiles.

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